IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application — Confirmation No. 1980

Inventors: Kurt Lang et al. — Group No.: 1643

Application No. 10/529,090, filed September 30, 2005 Examiner: Bradley Duffy
(Case Docket No. **20968 US**)

For: **CONJUGATES OF INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-4 AND POLYETHYLENE GLYCOL**

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Kurt Lang, declare that:

Background

1. In 1985, I received a diploma in biology from Regensburg University, in Regensburg, Germany. In 1988 I received a Dr. rer. nat. degree in biology from the University of Regensburg, Germany. For my PhD thesis, I investigated the molecular mechanism and enzymatic catalysis of slow protein folding reactions.

2. A summary of my various positions in academia and industry, as well as a list of my publications, is provided in my *curriculum vitae*, a copy of which is attached hereto as Exhibit 1.

3. Since 1998, I have been employed as a scientist at Roche Diagnostics GmbH ("Roche"). During my tenure at Roche I have held several positions, the most recent as head of protein sciences. Since October 2009, I have been

responsible for high throughput protein purification for lead and cell line selection, supply of discovery projects with research tools, antigens and lead candidates, technical evaluation of new protein formats, development of down stream processes for clinical candidates, supply of GLP toxicology studies and transfer of purification processes to technical development for GMP manufacturing.

4. I am familiar with the subject matter of the captioned patent application, filed on September 30, 2005. The experiments reported in the captioned application were conducted under my supervision and control as head of the project team.

5. I am also familiar with the subject matter of Ashkenazi et al., Cox et al., Francis et al., Byun et al., Veronese et al., and Monfardini et al., which were cited by the Examiner in the Office Action of January 21, 2010 in the captioned application.

6. I am also familiar with the animal-based experiments reported in the captioned application.

7. I make this declaration in support of applicants' position that the biological activity of the 40 kDa-PEGylated IGFBP-4 conjugates encompassed by the claims of the captioned application is significantly and unexpectedly superior to that of 20 kDa-PEGylated IGFBP-4.

Discussion

1. I base my analysis and conclusions upon the data found in the captioned application.

2. The data were generated by performing experiments that were under my supervision and control as head of the responsible project team.

3. The experimental details are set forth in Examples 13, 14 and 15 of the above-captioned application, entitled "Serum Kinetics of IGFBP-4 Derivatives", "Antitumorigenic Effect of IGFBP-4 Derivatives in the PancTu-1 Orthotopic Pancreas Cancer Model" and "Influence of PEGylated IGFBP-4 on Normal Kidney Cells/Kidney Organs," respectively.

4. The results for the Example 13 showed that by daily application of IGFBP-4, monoPEG20-IGFBP-4, and monoPEG40-IGFBP-4 to mice only monoPEG40-IGFBP-4 accumulated in serum.

5. The results for the Example 14 showed that:

(1) both tumor markers assayed (CA19.9 and Cyfra 21.1) were significantly reduced by treatment with monoPEG40-IGFBP-4 but not by treatment with monoPEG20-IGFBP-4; and that

(2) chronic administration of monoPEG20-IGFBP-4 did not inhibit tumor growth, as it was found that mean tumor volume at termination was 287 mm3 and very similar to the control group receiving only PBS (226 mm3) whereas in contrast, treatment with monoPEG40-IGFBP-4 reduced tumor growth, with mean tumor volume calculated at 163 mm3 for the monoPEG40-IGFBP-4 treatment group. The CA19.9 and Cyfra 21.1 tumor marker results are shown in tabular form in Tables 2 and 3 on page 29 of the application as filed and on page 10 as published.

6. The results for Example 15 showed that chronic treatment with mono-20 kDa-PEG-IGFBP-4 applied s.c. or i.p. induced moderate to severe histopathological alteration of kidney tissue. Cells belonging to proximal tubules were vacuolated without sign of inflammation and necrosis. These findings were not observed after s.c. or i.p. application of mono-40 kDa-PEG-IGFBP-4.

Based upon the foregoing, the following conclusions are apparent:

7. From the data presented in Examples 13, 14 and 15 it can be seen

(1) that only with a monoPEG40-IGFBP-4 therapeutically effective serum levels can be obtained, and

(2) that only with monoPEG40-IGFBP-4 a reduction of the tumor markers CA19.9 and Cyfra 21.1 can be seen, and

(3) that with monoPEG20-IGFBP-4 severe histopathological alterations of kidney tissue are induced.

These findings were absolutely surprising as the in vitro binding experiments showed that IGFBP-4 and monoPEG20-IGFBP-4 as well as monoPEG40-IGFBP-4 showed IGF-binding and inhibition of IGF-I receptor phosphorylation whereas only monoPEG40-IGFBP-4 showed also an effect in vivo which in contrast was not seen for monoPEG20-IGFBP-4. At the same time it was also surprising that monoPEG20-IGFBP-4 did not accumulate in blood serum whereas monoPEG40-IGFBP-4 did. And finally most surprisingly and absolutely unexpected was that monoPEG20-IGFBP-4 caused severe histopathological changes in kidney tissue which were not observed for monoPEG40-IGFBP-4.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

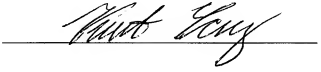
Date 05/17/2010 

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Exhibit 1

Curriculum vitae

Kurt Lang

Date of birth:	April 10th, 1958
Place of birth:	Amberg, Germany
Nationality:	German
1985	Diploma in Biology, University of Regensburg, Germany
1985-1988	Doctoral.-Thesis at University of Regensburg, Germany: Mechanism and enzymatic catalysis of slow protein folding reactions
1988-1990	Senior Scientist, Protein Chemistry Biotechnology Department BASF AG, Ludwigshafen, Germany
1990-1998	Senior Scientist, Biochemistry R&D Biotechnology Boehringer Mannheim GmbH, Penzberg, Germany
1998-2002	Senior Scientist, Biochemistry Pharma Research Oncology Roche Diagnostics GmbH, Penzberg, Germany
2002-2003	Program Manager Biopharmaceuticals Research Pharma Research, Biologicals R&D Roche Diagnostics GmbH, Penzberg, Germany
2003-2007	Head of Process Research Pharma Research, Biologicals R&D Roche Diagnostics GmbH, Penzberg, Germany
2007-2009	Head of Process Research and Supply Pharma Research, Biologicals R&D Roche Diagnostics GmbH, Penzberg, Germany
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Publications:

Lang, Kurt; Schaubmar, Andreas; Schleypen, Julia; Schlothauer, Tilman. Pegylated insulin-like-growth-factor assay, WO 2009/121551

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